IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Application Serial No. 09/837,562	Group Art Unit: 1623
Filing Date: April 19, 2001	Examiner: McIntosh, Traviss C., III
For: Composition And Method For Normalizing Impaired Or Deteriorating Neurological Function	Docket No.: 012439.0104PTUS (Formerly 12439.101B)
	Confirmation No.: 7515
Inventor: Edward Larry McCleary	Attachment to Paper No. 14

DECLARATION OF JAN F. BAUMGARDNER, M.D.

I, Jan F. Baumgardner, hereby declare:

1. I have been a licensed physician for forty years. My primary practice has been as a Board Certified Family Physician since 1968, though I have been residency trained and very active in occupational medicine since 1983. A copy of a brief version of my resume is attached as Exhibit A. All statements made herein of my own knowledge are true, and all statements made on information and belief are true to the best of my knowledge.

2. I have read the above-designated patent application (hereinafter "the Application"), the Office Action mailed July 28, 2003 (hereinafter "the Office Action"), and the Advisory Action dated December 16, 2003. I have also read the current claims in the Application.

3. I submit this Declaration to present to the Examiner, in an authenticated manner, facts concerning the patentability of the current claims.

4. I should first point out that I am neither a neurologist nor do I have a Ph.D. in therapeutics for neurological disorders as mentioned by the Examiner on page 7 of the Office Action.

5. I consider myself an average medical generalist, who has tried to keep up with the journals throughout his career. For example, I regularly volunteer to serve as a temporary family physician in rural communities in Colorado which have a sudden

need. I take care of routine and complex family medicine matters and emergencies, but, for example, insist that newborn and infant intensive care, and complicated obstetrics be transferred promptly to a regional center as I am not current in these types of case. On the other hand, I am more comfortable with acute and chronic, work related or not, injuries and toxicology than the average FP, which includes neurological and orthopedic injuries. I have, I think, been a little more interested than the average FP in preventive health and treatment using alternative and nutritional means – perhaps because I live in Boulder, Colorado! All the major medical journals have emphasized these treatment alternatives for the last decade, encouraging general physicians to always ask ill patients if and what such treatment they are using, both to avoid adverse reactions and to be involved directly with patients who choose them.

6. The Examiner's objection or objections to the claims are not entirely clear. I have read the Office Action and the Advisory Action many times, and it appears to me that the Examiner is saying that one skilled in the art of preparing compositions for treating neurological conditions could not read the Application and prepare a composition including:

(A) at least one agent which promotes synthesis of ATP and/or creatine phosphate in the body;

(B) at least one antioxidant for scavenging free radicals in at least one pathway in the body;

(C) at least one agent for treating or maintaining membrane function and structure in the body;

(D) at least one agent for treating or maintaining normal neurotransmitter function in the body;

(E) at least one agent for down-regulating cortisol action; and

(F) at least one agent for suppressing activation of apoptotic pathways in the body;

which composition is *efficacious* in treating a particular impaired or deteriorating neurological function in the patient being treated.

7. I put the term *efficacious* in italics because that seems to be the heart of the Examiner's objections. That is, at page 8 of the Office Action, just before the heading "The existence of working examples", the Examiner agrees that one skilled in the art could read the Application and create many examples of the composition, but indicates that "one skilled the art would not come to the conclusion that the compositions would have efficacy in treating any and all neurological disorders".

8. I prefer to state the issue in the following way: Could one skilled in the art read the patent application and create a composition that would have efficacy in treating a particular impaired or deteriorating neurological function?

9. I state the issue in terms of an impaired or deteriorating neurological function, rather than treating "any and all neurological disorders" because that is what the claims state, and there is a difference between the two. I state the issue in terms of a particular neurological function because I and other physicians always treat one patient at a time.

10. I will first address the part of the issue regarding whether a physician such as myself could read the Application and create a composition as specified in A) through F) in paragraph 6 above, and then I will address the *efficacy* part of the issue.

11. With regard to whether a physician, such as myself, can read the Application and prepare a composition as specified in A) through F) in paragraph 6 above, the simple answer is "yes".

12. I fully understand each of the items A) through F) in paragraph 6 above, as anyone who has stayed current in the medical literature would. I also am familiar and comfortable with ninety-five percent of the specific ingredients described in the Application, such as those listed in the table on pages 25 through 27 of the Application. The few that I am not familiar with, I am sure I could research quickly on the Internet.

13. That is not to say that the composition as described in claims 1 and 24 is conventional. It is certainly a novel way of treating impaired or deteriorating neurological function.

14. In fact, my first impression when I skimmed the application was that it was so unconventional that I might be dealing with another one of the less than scientific medical treatments that seem to arise spontaneously in Boulder, Colorado.

15. However, as I read the Application in detail, I started having one "aha!" after another as I understood it, and when I had fully understood what Dr. McCleary had created, my reaction was "why didn't I think of that."

16. Of course, the reason Dr. McCleary rather than I thought of this is that he is a pediatric neurosurgeon, which, in my view, is a very complex and difficult area of neurological practice.

17. I also understand that about six years ago, Dr. McCleary collapsed while making his rounds at Children's Hospital in Denver. After that, he could no longer practice neurosurgery, for obvious reasons, and since then has focused on learning and understanding the root causes of impaired or deteriorating neurological function.

18. This is what permitted him, and not I, to develop what I now consider to be a fundamental prescription for treating impaired or deteriorating neurological function, which prescription is succinctly summarized in claims 1 and 24 of the Application.

19. As I read the Application, I realized that a good deal of thought and advanced knowledge of neurological function had gone into it.

20. Instead of focusing on the symptoms of a specific disease, as do the vast majority of journal articles in neurology, Dr. McCleary has focused on the fundamental functions which are required for healthy nerve and brain cells.

21. One "aha!" that I particularly remember is the one that occurred when I read the item E) in the prescription: "at least one agent for down-regulating cortisol action".

22. The conventional wisdom when I was learning medicine, which still persists with many physicians today, is that adrenocorticosteroids I are good, and the more cortisol the better.

23. However, the literature has emphasized what practitioners have learned through experience: that repeated exposure to increased cortisol (the body's reaction to physical emotional and other stress) results in many debilitating effects. Dr. McCleary has rightfully recognized that the underlying reason for the debilitating effects is the destructive effect of cortisol on the nerve cell. I did not fully realize this until I read the patent Application.

24. The Examiner states in the Advisory Action that the claims should be written in "nomenclatorially/formalaically/structurally identities" for the components of the composition, or alternatively, should claim a particular combination of components. I think this would be less clear than the form that the claims are now in.

25. The reason I think the claims are more clear in their present form is that I know, for example, what an "agent which promotes synthesis of ATP and/or creatine phosphate in the body" does. Given this description, I can select from the examples in the specification or, more likely, use my own knowledge of specific examples of agents which promote synthesis of ATP and/or creatine phosphate in the body, and select one that I think is best for the particular patient I am treating. An individual patient's abilities to absorb and process nutritionals and medication vary greatly – using short acting forms frequently versus long acting forms will vary depending on the patient.

26. For example, I may know that a particular patient had had an adverse reaction to vinpocetine in another instance, and that he or she had positive results with co-enzyme Q 10 in a previous treatment, so I would prescribe for that patient co-enzyme Q-10 as the agent which promotes synthesis of ATP and/or creatine phosphate in the body.

27. Or I may simply choose the one of the possible agents which promotes synthesis of ATP and/or creatine phosphate in the body that I am most familiar with.

28. Or some new agent that promotes synthesis of ATP and/or creatine

phosphate in the body may become available, and I may prefer to use that agent.

29. As the Examiner states at the bottom of page 6 of the Office Action, there is a wide variety of parameters that a physician would consider in prescribing a treatment. Stating the prescription in terms of the specific functions of the agents allows me to select an appropriate particular agent for a particular situation so as to best arrive at the prescribed function in view of all the various parameters.

30. I could say a lot more about why I am impressed with the thought that went into the Application and how the way the claims are currently phrased coincides with how medicine is practiced, but the Examiner has already admitted that one skilled in the art can make a composition as specified in claims 1 and 24, so I will now focus on whether the composition would be efficacious.

31. In my opinion, a composition made according to the prescription in claims 1 and 24 would be efficacious.

32. Agents A), C), and D) each relate to a fundamental requirement of any nerve cell. If ATP or creatine phosphate is supplied, membrane function and structure is healthy, and neurotransmitter function is maintained, the physician has gone a long way towards avoiding neurological disease.

33. However, Dr. McCleary also recognizes that there are also certain processes that occur within a normal body that must be prevented if nerve cells are to remain healthy. Items B), E), and F) address these processes.

34. If each of agents A) through F) are fully effective in providing the function indicated, and the medical literature indicates that agents, as summarized in the Application, that provide each function exist, then I would estimate that, in theory, the invention would be efficacious for 70% to 90% of neurological dysfunctions.

35. In addition, the specific ingredients suggested in the Application are nearly universally non-toxic or there is a very wide margin between the effective therapeutic dose and the harmful dose. To put this in perspective, there is only a 10% difference between the dose of digitalis that is therapeutically effective and the dose that is dangerous. In all cases for the ingredients recited in the Application that I am

familiar with, which is most of them, the difference is greater than 300%. Thus, the invention avoids problems that would argue against efficacy.

36. Further, the prescription in the claims is relatively simple for a physician to follow. In my opinion, this prescription, and adjusting it for the many parameters that may arise in a particular patient, is simpler than, say, the task of guiding a patient through the complexities in cancer treatment or following the workers compensation guidelines (which can be very complex) for treating low back pain that does not resolve spontaneously. Thus, there is a likelihood that a physician can follow the prescription competently and effectively.

37. To analyze the issue of efficacy, one should understand the meaning of efficacy in medicine and neurology in particular.

38. There are many treatments in medicine that do not work very well but are considered to be efficacious. As one example, treatment for ulcers used to involve a complex combination of diet and lifestyle changes to avoid stress, plus a choice of many different medications. This treatment, except for rest away from the stresses of daily life, did not result in full remission in most cases, and ulcers were essentially a lifetime affliction with multiple recurrences, often needing surgical and radical treatment to stop life-threatening bleeding or prevent chronic ulcers from becoming cancerous.

39. However, about fifteen years ago a practicing physician (which is why I like telling this story) discovered that most ulcers were due to a bacteria, Helicobacter Pylori. Now ulcers are quickly cured with medicines that eradicate this organism.

40. However, there are still some doctors that continue with the old ulcer treatments, even though modern medicine has proven them to be essentially irrelevant to the condition. These doctors would, of course, say the treatment is efficacious.

41. The practice of Clinical Neurology is still, in some respects such as degenerative disease, at the stage ulcer treatment was fifteen years ago. For example, it was considered until quite recently that neurons in the brain do not regenerate. Remarkable new treatments in the physical therapy of strokes have come

about, a striking example of which is: instead of encouraging vigorous relearning of tasks with unaffected extremities, we now bind down the unaffected extremity so that the patient HAS TO USE the affected side, which has been shown to promote regeneration.

42. Although there are documented cases where nerves have, in fact, regenerated, it does not always happen. Why they have is not understood, and they cannot be regenerated reliably.

43. Any good scientist, in my opinion, would have to admit that if nerves have regenerated in some cases, then, in fact, they can be regenerated, and the reason that they do not regenerate in most cases is because we do not yet understand how to do it.

44. Similarly, most drugs that are used in neurology, such as Aricept™, have very low efficacy, but, they are used because they are currently all we have, in spite of the dangers of toxicity.

45. Based on all of the above, it is my considered opinion that a composition based on the prescription in claims 1 and 24 of the Application would definitely be efficacious in the sense that the term is used in neurology.

46. However, ultimately, in medicine, the proof of efficacy is in the results obtained.

47. I have received a copy of a Draft Executive Summary and Final Report on a clinical study of the efficacy of the composition as described in claims 1 and 24, a copy of which is attached as Exhibit B.

48. I am familiar with clinical studies, and the results summarized in this report are well stated.

49. The products tested included at least one ingredient from each of the groups A) through F) of claims 1 and 24.

50. The design of the study was prospective, randomized, placebo controlled, and was triple blind. Thus, the study conforms to the highest standards for clinical studies.

51. The methods of the test, such as VIGIL, CVLT-II, and the Beck Depression Inventory Test are the traditional tests that neuropsychologists use to test the various defined aspects of nerve and brain function.

52. In nearly every case, the difference between the result for the persons on the placebo and the persons on the product were large.

53. The P values were generally 0.10 or lower, which means that the results were statistically significant. In cases where the P values were higher, it is evident that this was due to the fact that the study is not yet large enough to scientifically arrive at a statistical valid result. There is no reason from the study to think that as the study is expanded to a larger group, that less good results would be obtained.

54. I agree fully with the conclusions on page 23 of the report, that the results of the study were impressive.

55. If these results hold up in future studies, the instant invention is a true breakthrough in neurology. I have no reason to believe that the results will not hold up, and, based on this clinical study, until shown otherwise, I will consider the invention to be efficacious in treating impaired or deteriorating neurological functions, and plan to it in my practice, as it would be cruel to deteriorating patients not to use it; particularly since the defined toxicity of this invention is less than increased doses of currently marketed, and not very effective pharmacological agents.

56. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001, and that such willful false statements may jeopardize the validity of the Application or any patent issued thereon.

27 January 2004
Date

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Education

- University of Detroit, BSEE
- Wayne State University, College of Medicine, Detroit, MD
- UCLA, Westwood, Los Angeles, Rotating Internship
- L.A.County, Harbor General, ob-gyn/peds
- Graduate School of Public Administration, University of Colorado
- University of Cincinnati, Kettering Institute, Residency in Occupational Medicine

Exams,Certifications, Awards

- National Board of Medical Examiners
- American Board of Family Practice
- Level II Occupational Medicine Certification, recert 2001
- Life Fellow, American Academy of Family Practice, 1980
- Physician Recognition Awards, AMA (six awards, most recent 1998)
- ACOEM/AAMRO , Medical Review Officer, 1996-97

Experience

- Peace Corps Staff Physician/Medical Director, Latin America/Caribbean, 1967-69
- Private Practice, Family Medicine, Boulder, CO 1969-78
- Various Academic Appointments as Instructor, Assistant and Associate Professors, Medex Program, University of Utah School of Medicine, Univ. of Maryland College of Medicine, Univ of Colorado Medical School and Residency Programs in Colorado
- Corporate Medical Director, Storage Tech Corp., Louisville, CO 1978-83
- Private Practice/Independent Contractor, Occupational Medicine, 1984-Current (recommendations from contracted agencies and physicians available on request)
- I continue to keep current in General Medicine through volunteer and locums assignments on a regular basis, in addition to continued academic studies

Memberships: Boulder County and Colorado Medical Societies, American Medical Association, American Occupational Medicine Association, American and Colorado Academies of Family Practice, Docs Who Care, Torch International, SPEBSQSA.

Other: Native of OH, Resident CO 30yr, Speaks fluent Spanish and some German Enjoy Music and Chorus singing, Bicycling, Foreign Travel, Science and Philosophy

EXHIBIT A

Executive Summary and Final Report; Protocol, Methods, Results, and Conclusions

Prospective, Randomized, Placebo-Controlled, Triple-Blinded Clinical Trial to Test the Efficacy and Short-Term Safety of *Cognidex*™, a Natural Herbal Supplement Intended to Improve Memory, Concentration, Focus Cognitive Functioning, and Reduce Anxiety and Depression

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EXHIBIT B

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December 29, 2003

Clinical Site:

Bangor, Maine:
Marshall-Blum: Clinical Outcomes Specialists (parent company)
Herbal Research Clinic
Independent Medical Research Center
James M. Blum, PhD, Study Coordinator, Epidemiologist and Biostatistician
Medical Director: Ronald I. Blum, MD
Medical Advisor: Felix Hernandez, MD

Protocol

Objectives

To study the efficacy and short-term safety of Advanced Metabolics' Cognidex™ and Brain Powder Drink Mix in human subjects.

Design

- Prospective, randomized, triple-masked, placebo-controlled, parallel-group clinical trial;
- This study will be divided into 2 phases. For Phase 1, the duration of the trial will be 3 months on Cognidex™ active product or placebo. An analysis will be completed at the end of this period comparing the treatment group to the control;
- For Phase 2, all subjects who were randomized to and completed the placebo treatment in Phase 1 will complete an additional 2 week open label assessment of the Brain Powder Drink Mix;
- This trial had Institutional Review Board (IRB) approval (Due to FDA guidelines, details are only available upon request);
- Randomization determined who was on placebo and who started with the active product; Unequal number of subjects were randomized for both the active and placebo groups; for every two subjects randomized to take the placebo, three subjects were randomized to take the product;
- The duration of the trial was for three months on the active product or placebo;
- Subjects were recruited from general population of the greater Bangor, Maine region;
- Subjects were paid $100 for completion of their participation in this trial;
- This clinical site is an independent research facility;
- All subject contact was with a study coordinator or research nurse who was blinded to the randomization scheme;
- A registered nurse will see all subjects at each visit.

Subject Selection

Inclusion Criteria:

- Women and men expressing interest in taking part in a trial assessing the products and experiencing symptoms of cognitive dysfunction;
- Subjects who are ages 30-75;
- Subjects who passed a compliance screening test;
- Subjects who passed a health screen;
- Subjects able to tolerate the active product and placebo;
- Subjects who signed an IRB-approved consent form;

Exclusion Criteria:

- Subjects who are non-compliant with testing and treatment regimens;
- Subjects who express problems with ingredients in the active products or placebo;
- Subjects under the age of 30 or over the age of 75;
- Subjects with moderately severe co-morbid disease, that includes cardiac, pulmonary, renal, hepatic, or active cancer (this determination is subject to the study physician);
- Subjects who are currently taking or have taken within the past 30 days any medications or other dietary supplements for the treatment of cognitive dysfunction or similar disorders;
- Subjects with alcohol abuse as determined by provider interviews or medical history indicating the consumption of >6 standard alcoholic drinks per week;
- Subjects who are nursing, pregnant, or trying to become pregnant;
- Subjects with insulin dependent diabetes;
- Subjects with uncontrolled hypertension;
- Subjects with diagnosed mental illness or conditions that would complicate the primary outcome measures;
- Subjects with significant head, neck or spinal injuries;
- Subjects with diagnosed or suspect seizures;
- Subjects with diagnosed or suspected manic depression;
- Subjects with kidney disease;
- Subjects with liver disease;
- Subjects with any tendency to develop kidney stones;
- Subjects with bi-polar disorder, schizophrenia, moderate to severe depression or similar psychological conditions;
- Subjects with a soy allergy;
- Subjects taking sulfa based drugs;
- Subjects taking calcium channel blockers;

Additional Exclusions:

- Subjects taking cardiac glucosides;
- Subjects taking MAO inhibitors;
- Subjects taking Dilantin or Penicillamine;
- Subjects taking warfarin (coumadin), heparin, levodopa, more than 2 aspirin per day or similar blood thinning drugs.

Cautionary Criteria:

- Subjects with any medical conditions;
- Subjects who are taking any prescription medications, over-the-counter medications and/or any dietary supplements.

Confounding Factors:

- Gender
- Age
- Body Mass Index (BMI)
- Alcohol consumption
- Prior treatments for cognitive dysfunction or similar disorders
- Baseline level of mental function
- Psychological problems or diagnoses
- Medical Status or current medications

Compliance Test and Standards:

- Subjects must complete their questionnaires in a timely manner;
- Subjects must take their assigned treatment according to the instructions.

End-Point / Outcome Measures

Primary End-Points / Outcomes:

- Ability to focus
- Ability to concentrate
- Cognitive function
- Improved memory
- Assess distraction

- Sleep Quality Parameters
- Energy and Fatigue
- Quality of life and general health measures including selected portions of the SF-12 (Quality-of-Life)

We used selected portions of John Ware's SF-12 Quality of Life questionnaire to reflect general medical and psychological well being. The SF-12 is an established tool that has been used in many published research articles and will be useful in this context.

Secondary End-Points / Outcomes (Safety Parameters):

- Adverse Events
  - Serious
  - Minor
- Systolic Blood Pressure
- Diastolic Blood Pressure
- Pulse
- Respiration
- Weight

Other End-Points / Outcomes:

- Protocol Compliance
- Continue to Use the Product

Questionnaires:

- Intake Form
- Initial Visit Form
- Demographic Form
- Subject Evaluation Form
- Nurse Evaluation Form
- Neuropsychological Testing Forms
- End of Phase 1 Form
- End of Phase 2 Form

Product Usage

- Subjects consumed a total of four tablets daily;
- All tablets (4 in total) taken in the morning;
- Tablets taken with a glass of water;
- Tablets taken on an empty stomach half an hour before a morning meal.

Instructions were given so that subjects did NOT take their assigned product within two (2) hours of any antibiotics or mineral oil because it (product) might affect absorption and/or concentration.

Placebo Product

The placebo was similar in appearance (size, shape, color) to the actual product except that it only contained inert substances. Both were dispensed in unlabeled white bottles.

Masking:

Marshall-Blum trials are triple-masked by virtue of masking the subject, the research staff, and the biostatistician. The identity of the specific treatment or placebo arm is not available to the research nurses or biostatistician, unless a medical emergency arises. We use a multi-step process that assures this confidentiality. One of two study coordinators prepares the product bags that are given to each subject. Each bag is marked with a number that includes the study number and specific subject number. For example 34023 would be decoded as study number 34 and subject number 23. The study coordinators keep secured records as required by the IRB that includes the randomization scheme, subject identifiers, and other pertinent information. This information is kept from the nurses and biostatistician. In cases of medical problems the consulting physician or nurse acts without knowledge of the randomization. However, if the medical condition is considered 'serious' the code may be broken. The IRB and the study sponsor will be notified under these circumstances as required by law.

Protocol:

Subjects were recruited from the general population surrounding Bangor, Maine. They met the inclusionary and exclusionary criteria and passed a health-screening test. Subjects' were dropped during the study if they repeatedly failed the compliance standards involving dosing, medications or dietary supplements for this condition.

Upon completion and passing of the phone screening, the potential subject was scheduled for an initial visit at the Herbal Research Clinic in Bangor, Maine. At this initial visit, the potential subject was interviewed to help the study staff decide if they met all of the conditions to be in the study.

Subjects were initially interviewed by phone and subsequently screened into the study by a research nurse at the Herbal Research Clinic at 268 State Street. One of the nurses read and reviewed a consent form with the potential subjects. Once satisfied, the potential subject signed the consent form. Additionally the subject received a thorough health screen before randomization. They received instructions on how and when to complete the survey instruments and were given a one-month supply of product or placebo.

The potential subject had:

- Questions asked about their medical history.
- Questions asked about the medications and dietary supplements that they are currently taking.
- Questions asked about their habits, work environment and living conditions.
- Questions asked about their current condition and any treatment that they may have received.

The subject then:

- Was asked to complete a Demographic Form;
- Was asked to complete an Initial Visit Form;
- Had their height, weight, blood pressure, pulse and respirations measured;
- Was given a 1-month supply of their assigned product.

The Study Coordinator instructed all subjects as to the protocol and other details of the study. Subjects were instructed precisely how and when to take the dietary supplements during the course of this study and how to report adverse reactions and any other pertinent information.

Subjects were randomized into either the placebo or active treatment group. The duration of the study was three months. All subjects randomized to receive the placebo were given a three-month supply of the active material for their own use after successfully completing the study.

They were required to come back to the clinic every month to have their blood pressure, weight, pulse, and respirations checked and complete a survey and then received an

additional one-month supply.. This procedure was repeated at the two and three-month mark.

Any adverse events were reported to Advanced Metabolics Research Group and to the IRB using appropriate reporting format.

Instructions to the Subjects

Cognidex™ or Placebo (for the first three months)

Take 4 tablets daily; 4 tablets in the morning with a glass of water on an empty stomach half an hour before a meal.

Do not take your assigned product within 2 hours of any medicines or dietary supplements because it may affect absorption and/or concentrations.

Brain Powder Drink Mix (for week 13 and week 14 if applicable)

Take 1 scoop daily; mix 1 scoop of powder with a 12 ounce glass of water in the morning and drink it 30 minutes prior to your morning meal.

- **Return to the office for visits at 1 month, 2 months, 3 months and 14 weeks** (if applicable) **after starting on your assigned product.** The questionnaires will be reviewed at this time. Measurements will be taken. Additional information will be handed out and questions will be answered at each visit.
- **Please report any difficulties with the product or ask any questions that you have as soon as possible.**
- **Please inform us of any change in your health status or medications immediately.**
- Bring your assigned product bottle with you for each visit.

Instructions to the Subjects Continues

Active Product Ingredients: *Cognidex™*: Betaine, ascorbic acid (vitamin C), ascorbyl palmitate (alternative form of vitamin C), vitamin E, thiamine hydrochloride, riboflavin, niacinamide, pyridoxine, folic acid, cobalamin, biotin, pantothenic acid, magnesium citrate monohydrate, L-taurine, Opti-zinc, L-selenomethionine, chromium polynicotinate, potassium aspartate, glucosamine hydrochloride, chondroitin sulfate complex, PABA (para-aminobenzoic acid), lycopene, choline bitartrate, DMAE (dimethylaminoethanol) bitartrate, vinpocetine, huperzine A, N-acetyl L-carnitine, N-acetyl L-tyrosine, potassium phosphate, L-glutamine, inositol, pyridoxal A-keto (alternative form of pyridoxine), grape seed extract, bilberry, pine bark extract, soy bean phospholipid complex, coenzyme Q10, lipoic acid, reservatol, soy flavones, green tea extract, ginkgo, vitamin D3, creatine monohydrate and calcium carbonate. *Brain Powder Drink Mix:* Sodium chloride, sodium bicarbonate, potassium phosphate, magnesium sulfate, magnesium citrate monohydrate, glucose, lipoic acid, lecithin, N-acetyl L-carnitine, betaine, choline citrate, huperzine A, chromium polynicotinate, L-selenomethionine, thiamine (vitamin B1), niacinamide, pyridoxine (vitamin B6), magnesium-creatine chelate (Albion Labs) and folic acid.

END – Thank you for your participation

METHODS SECTION:

Brief descriptions of the primary cognitive tests used in this trial follow:

VIGIL: Continuous Performance Test *

Simply described, the Continuous Performance Test, requires subjects to identify a "target" letter [letter 'k'] from among other serially and randomly presented "non-target" letters. All of the letters that appear are 72 point (about two and a half inches tall) so that relative eyesight should not be a confounder. The rate that the letters appear on a black computer screen, are uniform, but the frequency that the "target" letter appears is not consistent. The computerized test that we used lasts a total of eight (8) minutes. The subject and computer were placed in a quiet room lacking outside stimuli.

Clinicians and researchers have come to regard the VIGIL test as an instrument that assesses attention and the ability to focus. Attention, as now understood, has evolved as a series of differentiations of information processing systems and processes. Researchers have studied attention as a form of arousal, a form of information processing efforts, and as a concomitant effort, and believe that attention is not a unified single process. Thus, any given test of attention may only assess certain aspects of attention.

The results of the VIGIL are normalized to age and gender. A full discussion of the test may be found in the Appendix to this executive summary. Specific questions may be addressed to Dr. Hess at her office.

The four measures obtained from the VIGIL are the total correct responses, the number of misses (omissions of the "target" letter), the number of extra hits ("non-target" letters mistaken for the "target" letter), and the response time in milliseconds. These measures represent the difference between the subject's baseline and the three-month testing.

CVLT-II: California Verbal Learning Test *

The CVLT-II measures both recall and recognition of two lists of words over a number of immediate and delayed-memory trials. In the first five trials, the examinee is asked to recall words from LIST A immediately after each presentation of the list. LIST A is composed of 16 words, four words from each of four semantic categories. Words from the same category are never presented consecutively, which affords an assessment of semantic clustering, the most effective strategy for learning unstructured verbal information. An interference list (LIST B) of 16 words is then presented for one trial. The inference list is followed by short delay-free recall and short delay-cued recall trials of LIST A. A twenty minute delay occurs next, during which non-verbal testing takes place. After the non-verbal testing, long-delay free-recall, long-delay cued-recall, and yes-no recognition trials of LIST A are administered. The CVLT-II ends with a new,

optional forced-choice recognition trial that is given approximately ten minutes following the yes-no trial.

The entire testing procedure takes approximately one hour and is administered in a quiet room with a registered nurse specially trained to administer these tests, under the direction of Dr. Ann L. Hess.

Beck Depression Inventory Test *

Self-rated depressive symptom inventories have long played a role in the assessment of depression in adults. This tool is easy to administer, readily analyzable, and the interpretations are universally accepted. Since they quantify the severity of the entire depressive syndrome, it has been used for descriptive purposes, to assess treatment outcomes, to test research hypotheses, and to select research and clinical subjects.

Unlike the CVLT and the VIGIL, the results are not normalized, but are reported as raw scores. Thus, they are not adjusted for age and gender. Since the scores are differences between the baseline and end-of-study testing frames, they are useful for determining overall depression indexes.

(*) Virtually taken from the various testing manuals, introduction sections.

Methods for the VIGIL and CVLT-II

Z scores for each individual question or parameter were obtained from the testing procedures provided by the VIGIL and the CVLT-II. These Z scores were provided to the statistician by Dr. Ann L. Hess.

Differences for Z scores for a given parameter between the baseline and end-of-study were subtracted to create the primary outcome measures.

Example

VIGIL Omissions

Time	*Response*
Baseline	*0.23*
Final at 3-months	*0.58*

The subtraction of the responses yields a point improvement for this subject on this question:

0.58 – 0.23 = 0.35 point improvement

- The responses for the two groups (placebo and treatment) for each symptom were summed. This forms the basis of the results.
- Differences in the means between the treatment and placebo groups were analyzed using the t-test.

Percent Improvement (PI):

PI = [(Three-month – Baseline) / Baseline] * 100

From the example above:

Percent Improvement = (0.58 – 0.23) / 0.23 = 152%

Summary Variable

We created a summary variable consisting of all the primary end-points parameters for each test; the VIGIL and the CVLT-II. This approach is often used in medical research and allows for a global comparison involving the entire scope of outcomes. This summary variable was compared, as were the other variables.

Statistical Significance

These criteria were set prior to the analysis.

Highly Significant:	$p < 0.05$
Significant:	$p < 0.10$
Statistical Trend:	$p < 0.20$

Randomized, Placebo-Controlled, Blinded, Clinical Trial Results:

Subject Numbers

Seventy (70) subjects were randomized for this trial (40 and 30 respectively in each group). Twenty-six (26) subjects completed the product phase of this trial while fifteen (15) individuals completed the placebo phase of this trial.

All of those subjects not completing the trial were due to loss-to-follow-up. We follow a strict protocol of attempting to contact those subjects who miss appointments that included serial phone calls and letters.

Baseline Characteristics:

There were few statistical or notable differences between the treatment (product) and placebo groups with respect to clinically important baseline and demographic parameters (See Table that displays this data in the next section). These included age, baseline weight, body mass index (bmi) and other demographic parameters, behavioral variables (smoking, alcohol, and caffeine), socio-economic indicators, and disease-state risk profiles (diabetes, heart disease, pulmonary conditions, gastrointestinal conditions, and other organ-system indicators).

The exceptions included thyroid disease that were higher in the product group (15.6% vs. 0%, $p<0.11$ Fisher's Exact Two-Tail test, respectively), while age was higher in the placebo group (48.8 vs. 45.7, $p<0.21$).

We used a combinational risk profile that included all the medical parameters, Body Mass Index (BMI), and the highest cut-points from the behavioral categories (e.g., daily caffeine intake greater than 3 cups per day, current smoker, and alcoholic consumption greater than 1 ounce per day) to assess overall risk. This risk profile was slightly higher in those subjects randomized to the treatment group, both as a mean score and in categories. The mean risk score for those on treatment was 3.84 compared to 2.72 for those on placebo ($p<0.092$). The percentage in the high risk group (7 or more points) was 16.1 vs. 5.6 favoring those on product.

The baseline profiles of the cognitive profiles were also similar between the two groups (See data in the graph sections for individual parameters).

Overall, this data provides good evidence that the randomization worked properly and that potential selection biases were avoided.

Cognitive Parameters

Means represent the Differences from Baseline for their respective Z Scores (age and gender adjusted)

VIGIL

Parameter	Group	Mean	Std. Dev.	P Value
Hit Rate	Placebo	0.39	1.6	
	Product	0.88	2.2	
	Difference	0.49		0.45
Omissions	Placebo	0.16	1.1	
	Product	0.82	1.95	
	Difference	0.66		0.17
Commissions	Placebo	- 0.05	0.45	
	Product	0.50	0.85	
	Difference	0.55		0.01
Speed	Placebo	0.06	1.0	
	Product	0.54	1.35	
	Difference	0.48		0.20

Summary Variable: Sum of the above 4 parameters

Parameter	Group	Mean	Std. Dev.	P Value
Summary	Placebo	0.56	2.85	
	Product	2.75	4.5	
	Difference	2.19		0.064

Comments:

The sum of the VIGIL questions is comprised of all the VIGIL questions. These include the following questions:

- Hit Rate
- Omissions
- Commissions
- Response Speed

The summary variable approach is considered a standard technique in the medical literature. Risk analysis and risk management has become so commonplace that it has reached the American lexicon. Most people know that a collection of symptoms represent a risk for the development of a disease or indicate that an individual is having a bad outcome. Take for example, the risk for developing heart disease or the factors that indicate one is having a heart attack. Physicians use these collective approaches because

single parameters are often lacking (negative) for a diagnosis. We use the summary approach in the same fashion. The summary variable actually provides a superior indicator than individual parameters because it represents the whole picture and minimizes individual variability.

The averages for each set are comprised of subjects reporting both negative and positive results. For example, subjects on product at the three-month mark compared to their baseline, had a mean of 2.75 points for the VIGIL Summary Variable, and had a range from -10.1 to 9.4 points. For the vast majority of product subjects, there was a steady improvement in cognitive parameters from the beginning of the trial throughout the three months.

CVLT-II

Parameter	Group	Mean	Std. Dev.	P Value
Total Response	Placebo	0.26	0.7	
	Product	0.91	0.8	
	Difference	0.65		0.01
Trial 1	Placebo	0.41	1.7	
	Product	1.74	1.3	
	Difference	0.66		0.006
Trial 5	Placebo	0.06	0.8	
	Product	0.33	0.7	
	Difference	0.25		0.25
Slope	Placebo	- 0.28	1.4	
	Product	- 1.04	1.3	
	Difference	0.76		0.085
Trial B	Placebo	- 0.03	0.8	
	Product	0.30	1.1	
	Difference	0.33		0.32

Parameter	Group	Mean	Std. Dev.	P Value
STFR	Placebo	0.38	0.8	
	Product	0.41	0.7	
	Difference	0.03		N.S.
STCR	Placebo	0.44	0.7	
	Product	0.71	0.7	
	Difference	0.27		0.24
LTFR	Placebo	- 0.13	1.2	
	Product	0.56	0.9	
	Difference	0.69		0.43
LTCR	Placebo	0.22	0.6	
	Product	0.44	0.7	
	Difference	0.76		0.26
Recognition	Placebo	0.50	1.2	
	Product	0.38	0.8	
	Difference	0.12		N.S.
False Positives	Placebo	- 0.09	0.7	
	Product	0.09	0.6	
	Difference	0.18		0.33
Semantics	Placebo	0.48	1.2	
	Product	0.94	1.3	
	Difference	0.46		0.25
Serial	Placebo	- 0.21	1.2	
	Product	- 0.46	1.6	
	Difference	0.25		N.S.
Primary	Placebo	- 0.06	1.0	
	Product	- 0.44	0.9	
	Difference	0.38		0.23
Intrusion	Placebo	- 0.43	1.6	
	Product	0.07	1.0	
	Difference	0.50		0.20

STFR: Short-Term Free Recall
STCR: Short-Term Cued Recall
LTFR: Long-Term Free Recall
LTCR: Long-Term Cued Recall

Beck Depression

Means represent the Differences from Baseline

Group	Mean	Std. Dev.	P Value
Placebo	0.69	5.0	
Product	4.31	6.2	
Difference	3.62		0.05

Anxiety

Means represent the Differences from Baseline

Group	Mean	Std. Dev.	P Value
Placebo	- 2.44	8.0	
Product	5.74	10.2	
Difference	8.18		0.009

Mood (Sum of the Beck Depression Scale and the Anxiety Score)

Means represent the Differences from Baseline

Group	Mean	Std. Dev.	P Value
Placebo	- 1.75	10.7	
Product	9.89	14.8	
Difference	11.64		0.009

Comments made by Dr. Ann L. Hess on the results of this trial.

VIGIL

Omissions:

The subjects on product were slightly more alert than those on placebo, missing far fewer of the target stimuli. They were able to focus and sustain their attention better on product.

Commissions:

There were fewer false-positive responses by the group on product than placebo. This suggests that they were better able to inhibit the impulse to respond inappropriately. This impulsiveness is a common feature of people with the hyperactive type of attention deficit disorder. [Note: See also the comments below about CVLT intrusions.]

Response Time:

There was a tendency for the product group to respond more quickly to the targets, and this indicates greater activation and more efficient (faster) information processing.

Overall:

Attention, focus, and concentration was sharper and more efficient for the product group than those on placebo.

CVLT-II

Overall Scores (Cumulative Trials 1 through 5)

Overall learning (information that can be stored and retrieved from short-term storage, while being actively processed) was better for those on product. This difference was significant, and large enough that it may have practical, real-world significance.

Trial 1:

The differences discussed above in overall learning appear to be largely accounted for by the initial registration of the list, suggesting that there was a strong effect for attention and concentration, or "working memory." Since other data indicates that there was no significant effect for primacy or recency, short-term or long-term recall, or use of strategies, this role of improved concentration is more likely.

Slope (improvement from Trial 1 to Trial 5):

There was more improvement across trials, showing better learning with practice, for those on product compared to those on placebo. The product subjects were able to get the information into short-term storage more efficiently, perhaps due to improved concentration.

Intrusion Errors:

There was a trend for the product group to make fewer errors of intrusion – including items that were not in fact on the lists – than the placebo group. This suggests that the product subjects were better able to self-monitor their own responses, and inhibit incorrect ones better than the placebo subjects. Intrusion errors are akin to the VIGIL commission errors discussed above. This second finding of a similar phenomenon lends even greater credibility to the hypothesis that this product helps people regulate cognitive functions and behavior more effectively.

[Note: although not statistically significant ($p<0.20$), the intrusion-error difference has about the same p-value as the response-time variable, thus I felt it was worthy of comment].

CVLT-II Overall:

There appears to be an improvement of short-term cognitive registration and storage of information when using the product compared to those on placebo.

Additional Outcomes:

Energy Levels

Means represent the Differences from Baseline

Follow-Up	Group	Mean	Std. Dev.	P Value
2-Month	Placebo	- 0.03	1.77	
	Product	0.81	2.21	0.11
3-Month	Placebo	- 0.33	1.89	
	Product	0.90	2.03	0.028

Sleep Quality

Means represent the Differences from Baseline

Follow-Up	Group	Mean	Std. Dev.	P Value
2-Month	Placebo	- 1.13	2.33	
	Product	0.52	2.40	0.01
3-Month	Placebo	- 0.77	2.46	
	Product	0.52	2.29	0.06

Depression

The mean represent the Differences from Baseline

Follow-Up	Group	Mean	Std. Dev.	P Value
3-Month	Placebo	- 0.19	0.94	
	Product	0.12	0.78	0.20

Weight

The mean represent the Differences from Baseline

Follow-Up	Group	Mean	Std. Dev.	P Value
2-Month	Placebo	- 0.13	3.9	
	Product	1.96	4.8	0.08
3-Month	Placebo	0.91	4.5	
	Product	4.25	12.0	0.20

Mean Arterial Blood Pressure, Pulse, and Respiration

Defined as: Baseline – Final Reading (3-month follow-up period)
Thus a positive number represents a decrease.

Indicator	Group	Mean	Std. Dev.	P Value
MAP	Placebo			
	Product			
Pulse	Placebo	- 0.11	10.6	
	Product	- 0.1.00	8.6	N.S.
Respiration	Placebo	0.78	2.9	
	Product	0.90	3.5	N.S.

Conclusions:

Summary:

In this trial, Cognidex™ demonstrated impressive improvements in all tested categories of brain function. These included memory, concentration, focus, cognitive functioning, depression and anxiety. The vast majority of subjects on Cognidex™ showed a steady improvement in mental performance throughout the trial. Cognidex™ also produced significant differences in both individual and combined test variables.

There were also significant improvements in daily energy levels and quality of sleep.

For the VIGIL testing, all four of the individual parameters as well as the summary variable were improved for those on product compared to those on placebo, with commissions being highly statistically significant, and omissions and response time meeting the criteria of a statistical trend. Attention, focus, and concentration were sharper and more efficient in those subjects on product and they tended to process information more rapidly.

The CVLT is a demanding test and results on it were equally impressive. Overall learning was improved and this effect was large and significant. Cognidex™ also enhanced working memory (short term registration and storage of cognitive information).

Improvement on mood, depression and anxiety scales were all highly significant.

There were few differences between groups with respect to the baseline characteristics.

There were no serious or adverse events reported to the IRB during the course of this trial to the IRB. There were no minor complaints that related to the product or placebo usage. Additionally, systolic and diastolic blood pressure, pulse, and respiration measurements did not significantly change from baseline and were not different than the placebo group. These factors indicate that the safety of the product is warranted but we caution that we cannot rule out the rare event during which a given individual might experience some unwanted, unpleasant or possible serious effects from the use of this product.

Appendix:

Testing Frames:

A set of risk factors will be collected at baseline on all subjects during the screening phase. This will include a medical history and behavioral (smoking, alcohol consumption) history, plus questions pertaining to their condition, symptoms, mental health and general health.

A nurse at baseline and at each visit will check weight, blood pressure, pulse and respirations. Height will be checked at baseline only.

For Phase 1, Questionnaires will be administered at clinic visits at baseline, 1 month, 2 months and 3 months.

Neuropsychological testing will be administered at clinic visits at baseline and 3 months (see Neuropsychological Testing).

There will be no diet or exercise requirements in this study.

There will be no laboratory testing administered in this study.

Neuropsychological Testing

Neuropsychological testing will consist of the VIGIL, CVLT, Beck Depression Inventory II/Anxiety Inventory for adults, which will be administered at baseline and 3 months at the Herbal Research Clinic. Herbal Research Clinic staff will be trained to administer neuropsychological testing by Dr. Ann Hess and Neuropsychological Services, P.A. of Bangor, Maine. Dr. Hess will be responsible for and oversee all neuropsychological testing (see Nutritional Supplement and Attention/Memory Functions).

There will be no follow-up questionnaire administered in this study.

In Phase 2, those subjects who were randomized to and completed the placebo arm of this study will evaluate the Brain Powder Drink Mix in an open label fashion for an additional 2 weeks. Weight, blood pressure, additional questionnaires, and an additional session of neuropsychological testing will be administered at 14 weeks.

This design is subject to changes by the Fox Commercial IRB.

Narrative:

Subjects will be recruited from the general population (see Recruitment).

A phone screening will be conducted to confirm basic qualification (see Intake Form). If potential subjects do not qualify at this or any other time, they will be told, given the reason and thanked for their interest and time.

Upon completion and passing of the phone screening, the potential subject will be scheduled for an initial visit at the Herbal Research Clinic in Bangor, Maine.

At this initial visit, the potential subject will be asked to participate in this study and sign a consent form (see Consent Form). Once the consent form is signed, the potential subject will be interviewed to help the study staff decide if they meet all of the conditions to be in the study.

The potential subject will have:

- Questions asked about their medical history;
- Questions asked about the medications and dietary supplements that they are currently taking;
- Questions asked about their habits, work environment and living conditions;
- Questions asked about their current condition and any treatment that they may have received.

The subject will then:

- Be asked to complete a Demographic Form;
- Be asked to complete an Initial Visit Form;
- Have their height, weight, blood pressure, pulse and respirations measured;
- Have neuropsychological testing conducted (see Neuropsychological Testing);
- Be given a 1-month supply of their assigned product.

The subject will be randomized (see Design and see Statistical Plan). The subject, the study nurse, the study physician and the principal investigator will not know which treatment is assigned.

The subject will be instructed on how to take the assigned product or placebo (see Dosing).

The subject will be instructed to report any changes in their medical condition, medications that they are taking, dietary supplements that they are taking or any possible side effects as soon as possible.

During this study, the subject will be asked to return to the clinic 3 times: 1 month, 2 months and 3 months after starting the study treatment. Those subjects who were randomized to placebo will be asked to return a fourth time (details below).

At the subject's 1-month and 2-month visit they will:

- Be asked to bring their bottle of study tablets;
- Have their weight, blood pressure, pulse and respirations measured;
- Be asked to complete a Subject Evaluation Form;
- Be given an additional 1-month supply of their assigned product.

At the subject's 3-month visit they will:

- Be asked to bring their bottle of study tablets;
- Have their weight, blood pressure, pulse and respirations measured;
- Have neuropsychological testing conducted;
- Be asked to complete an End of Study Form.

For subject's who were randomized to take product for the study, the 3-month visit will be their last office visit and they will not be required to take any more study product. The subject's participation in this study will end at this time.

For subject's who were randomized to take placebo for the study, the third office visit will be extended and a fourth office visit will be required.

At the placebo subject's 3-month visit they will also:

- Be given a 2 week supply of the Brain Powder Drink Mix.

The subject will be instructed on how to take the assigned product (see Dosing).

At the subject's 14 week (fourth) visit they will:

- Be asked to bring their product bottle;
- Have their weight, blood pressure, pulse and respirations measured;
- Have neuropsychological testing conducted;
- Be asked to complete an End of Study Form.

The 14 week (fourth) visit will be their last office visit and they will not be required to take any more study product. The subject's participation in this study will end at this time.

All subjects who complete all of the study visits and meet all of the study requirements will receive a free one-year supply of the active product and one hundred dollars as compensation.

Any side effects will be reported to Advanced Metabolics and to the Fox Commercial IRB (when serious and adverse) using appropriate reporting format.

Appendix 2: CLINICAL USE OF VIGIL

Professional Qualifications

Vigil can be administered and scored by a person who does not have advanced training in clinical psychology. However, in accordance with Standards for Educational and Psychological Testing (American Psychological Association, 1985) training in the administration of Vigil tests, and especially interpretation of Vigil tests, requires professional training in clinical psychology, neuropsychology, or a related discipline. Interpretation of Vigil results should only be provided by a professional with training and experience in clinical and neuropsychology or a related discipline.

Proviso for Test Use

In keeping with good clinical practice, clinicians should not use Vigil as the sole basis for a diagnosis. Clinicians and not computer programs should make diagnoses. Collateral evidence confirming hypotheses generated from Vigil in addition to other sources of data should always be considered in rendering a diagnosis.

Introduction

The practical and theoretical life of whole species, as well as of individual human beings, results from a selection which the habitual direction of their attention involves...each of us literally chooses, by his way of attending to things, what sort of a universe he shall appear himself to inhabit. –William James

Vigil is a proprietary version of the Continuous Performance Test; a test first reported by Rosvold (1956) for the diagnosis of brain damage. Simply described, the Continuous Performance Test requires subjects to identify a "target" letter (X) from among other serially and randomly presented "non-target" letters (non-X). Later revisions of the Continuous Performance Tests have added stimulus priming creating an AX test (Wohlberg and Kornetsky, 1973), increased cognitive loading in which subjects must examine more complex stimuli (Rutschmann et. al., 1977; Cornblatt et. al., 1988), and increased perceptual processing required in detecting blurred images

(Neuchterlain, 1983; Cegalis and Bowlin, 1992). New versions of the Continuous Performance Test have basically incorporated changes in stimulus type or complexity, use of different forms of stimulus degradation, and changes in timing of stimulus presentation and interstimulus intervals. The essential paradigm requiring detection of a target from among non-target stimuli has remained the same.

Clinicians and researchers have come to regard the Continuous Performance Test as an instrument that assesses attention. Attention, as a theoretical construct, has evolved as a series of differentiations of information processing systems and processes. Investigators have studied attention as a form of arousal (Mackworth, 1969), a form of information processing (Broadbent, 1971), and as concomitant of effort (Kahneman, 1973). The results of research efforts have yielded a consistent view that attention is not a unified single process. Rather, attention is a complex set of processes. Consequently, any "test" of attention can only assess specific forms or processes of attention.

Berlyne (1951), for example, differentiated two principle aspects of attention. "There are, first of all, intensive aspects which are a matter of how much attention the organism is given to the stimulus field as a whole. Then, there are selective phenomena which are a matter of how attention is distributed among elements in the stimulus field."

Research has provided justification for the view that CPT is a test of vigilance, or maintenance of attention over time. N.H. Mackworth (1957) defined vigilance as "a state of readiness to detect and respond to certain specified small changes occurring at random time intervals in the environment." As Mackworth and others have pointed out, vigilance, from the point of view of evolution, derives from the principle that change is dangerous. Adaptively, organisms ignore predictable and readily recognizable stimuli so that resources are ready to react to new and potentially dangerous or significant events.

The vigilance task was designed by N.H. Mackworth (1950). In the vigilance task, a signal is presented, and is fairly easy to detect. However, the temporal probability of the signal is so low and so variable that it cannot be learned. In the basic task, all changes in stimulation external to the task are reduced to a minimum. No feedback is given. The signal itself is selected from an unchanging, randomly changing, or respectively changing background.

In common daily activities, e.g. driving, cooking, and baby-sitting, vigilance is critical. In these situations, a person continuously monitors a variety of stimuli for the presence of particular kinds of information, i.e. critical signals or targets. A low

probability signal, when present, typically requires a judgment, an action, or further, more intense monitoring (where the stimulus is a complex stimulus string). It is intuitively obvious that vigilance in such tasks requires arousal and may be affected by differing states or mediators of arousal.

Kahneman (1973) has argued that "Arousal and effort are usually not determined prior to the action; they vary continuously, depending on the load which is imposed by what one does at any instant of time". Moreover, Kahneman argued that the continuous monitoring of stimuli in our environment requires some capacity even in our most relaxed conscious states. He termed this spare capacity.

Certainly, individuals in differing states of arousal may attend to or monitor stimuli differently. Kahneman summarized evidence for high arousal that suggested that in states of high arousal attention is narrowed, increasingly labile, more difficult to control, and changing in strategy. Conversely, low arousal may result in failure to adopt a task set and failure to evaluate performance. Kahneman's summary of attention in tasks that have interference is significant:

- Attention is limited, but this limit varies over time.
- Attention and effort exerted at a given moment depends on the demands of current activities.
- Attention is divisible, or allocable.
- Attention is selective and controllable

Vigil measures vigilance, or maintenance of attention over time. The vigilance required in Vigil tasks meets the defined criteria established by Mackworth. The flexibility in measure sand stimulus controls provided by Vigil also permit Vigil tests to be used to assess individuals who may vary in their arousal states, to assess changes in processing efficiency over time, to assess changes in processing as a function of stimulus complexity, and to assess changes in processing strategies over time (using signal detection measures that index liberality or conservativeness of judgement). Moreover, unlike many clinical or experimental measures of attention functions, the vigilance processes assessed in Vigil tests appear to have some ecological validity.

Development of Visual Vigilance Tests

Normative data have been collected for two visual versions of Vigil. The tests created in the Vigil environment vary from simple letter detection, to letter detection with priming. The parameters for each of these three tests are provided in Table 1.

Note that for each normed test, the stimulus color is white and the background color is black. Although Vigil permits you to vary stimulus or background colors, achromatic stimuli were used because they are replicable by a majority of users who have monochrome or color monitors.

Test Descriptions

Two visual CPT tests were used to develop estimates of normal vigilance. The tests were named, respectively, K and AK. Parameters for each test are presented in Table 1. In all tests, subjects were required to respond to the presence of the letter 'K': 'K' was the target. That is, a key press was required each time the letter 'K' was presented. The presence of an 'A' in the test name indicates that the task required that subjects respond to the letter 'K' only if 'K' was immediately preceded by the letter 'A'. 'A' served as a priming stimulus.

Whereas early CPT tests used the letter 'X' as a target, and 'AX' as the target sequence, Vigil uses 'K', following Kaplan's (1992) recommendations. Her reasoning is that the letter 'X' is unique and is the easiest letter to recognize; other letters contain similar component strokes and thus are more often confused.

Development of Normative Data for Visual Tests

Selection of Measurement Variables

Human Factors research has articulated several significant variables in vigilance tasks. The principle variables that index vigilance performance are Hit Rate, False Alarms, Errors of Commission, Errors of Omission, and Reaction Time. These variables were selected because they are well documented and supported by human factors research in vigilance (McGrath et. al., 1968 a, b). Recent research has also indicated that reaction time variability is also highly correlated with abnormal EEG results among ADHD children. Consequently, variability measures are included as important indicies of phasic changes in attention.

Vigil also provided research measures of vigilance. Nonparametric measures of signal detection, A' and H', are calculated. These measures require specific statistical assumptions about the nature of the detection task, responses, and the populations tested. The assumptions required may or may not be appropriate or necessary for clinical use.

Definition of Measurement Variables

Normative data for subjects without psychopathology, a history of head injury, or a history of psychopathology are presented for each principle variable in each test (K, AK) in Appendix A, Tables 15-20.

The definiton of test variables is presented below:

Hit Rate. This variable represents overall accuracy of target discrimination. The numerical value for this variable is derived by dividing the total number of targets correctly discriminated by the total number of targets presented.

False Alarm. This variable represents the extent to which the subject anticipates, incorrectly, the presence of a target when in fact no target was presented. The numerical value for this variable is obtained by dividing the total number of Errors of Commission by the total number of targets presented. Subjects with low false alarm rates can be said to be less impulsive and more accurate in their vigilance.

Errors of Commission. This variable represents the frequency of incorrect anticipations of targets presented, i.e., the subject responded as if the target was present when in fact no target was presented.

Errors of Omission. This variable represents the frequency of targets missed. The value of this variable represents the number of trials in which a target was presented and the subject did not respond.

Reaction Time. This variable represents the average time from the onset of each stimulus to the initiation of each response.

Perseverations. This variable represents the number of responses > 1.0 made during the interstimulus intervals. Vigil requires only one response to one stimulus. More than one response in the interstimulus interval is defined as a perseveration.